# CENTER FOR DRUG EVALUATION AND RESEARCH APPROVAL PACKAGE FOR: APPLICATION NUMBER NDA 21-437

Correspondence

# DIVISION OF CARDIO-RENAL DRUG PRODUCTS FOOD AND DRUG ADMINISTRATION



Woodmont II 1451 Rockville Pike Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number:

847-982-8152

Attention:

Dr. Donald Raineri

Company Name:

G.D. SearleLLC

Phone:

847-982-4751

Subject:

Inspra: Approval Letter with corrected labeling

Date:

10/8/02

Pages including this sheet:

22

From:

Daryl Allis

Phone:

301-594-5309

Fax:

301-594-5494

E-mail:

allisd@cder.fda.gov

PLEASE LET ME KNOW YOU RECEIVED THIS.

Daryl

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# **DIVISION OF CARDIO-RENAL DRUG PRODUCTS** FOOD AND DRUG ADMINISTRATION



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Phone:

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Fax:

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E-mail:

allisd@cder.fda.gov

PLEASE LET ME KNOW YOU RECEIVED THIS.

Daryl

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END=SEP-27 16:57

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301 594 5494- \*\*\*\*\*\*\*\*\*

# DIVISION OF CARDIO-RENAL DRUG PRODUCTS FOOD AND DRUG ADMINISTRATION



US Mull address: FDA/CDEH/HFT-110 5000 Fishers Lane Rockville, MD 20857

Woodmont II 1451 Rockville Pike Rockville, MD 20852

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Transmitted to FAX Number:

847-581-5179

Attention:

Dr. Donaki Raineri

Company Name:

G.D. Searle LLC

Phone:

847-982-4751

Subject:

Inspru: Approval Letter

Date:

9/27/07.

Pages including this sheet:

21

From:

Daryl Allis

Phone:

301-594-5309

Fax:

301-594-5494

E-mail:

alfisd@cder.fda.gov

Please call me to confirm that you received the letter.

It has been a pleasure to work you and your team.

Daryl





Food and Drug Administration Rockville, MD 20857

NDA 21-437

G.D. Searle LLC Attention: Donald L. Raineri, Pharm. D. 4901 Searle Parkway Skokie, IL 60077

Dear Dr. Raineri:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SC-66110 (Eplerenone) Tablets. Our December 17, 2001 letter referred to incorrect application and receipt dates. The correct dates are:

Date of Application:

November 28, 2001

Date of Receipt:

November 29, 2001

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 28, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 29, 2002.

We apologize for any inconvenience this may have caused you.

If you have any questions, please call:

Mr. Daryl Allis Regulatory Health Project Manager 301-594-5309

Sincerely,

(See appended electronic signature page)

Natalia A. Morgenstern Chief, Project Management Staff Division of Cardio-Renal Drug Products Office of Drug Evaluation 1 Center for Drug Evaluation and Research

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/s/

Natalia Morgenstern 1/4/02 04:40:14 PM



## DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration Rockville MD 20857

NDA 21-437

G.D. Searle LLC

Attention: Donald L. Raineri, Pharm.D

4901 Searle Parkway Skokie, IL 60077

Dear Dr. Raineri:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:

SC-66110 (Eplerenone) Tablets

Review Priority Classification:

Standard (S)

Date of Application:

November 29, 2001

Date of Receipt:

November 30, 2001

Our Reserence Number:

NDA 21-437

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 28, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 29, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Cardio-Renal Drug Products, HFD-110

Attention: Division Document Room

5600 Fishers Lane

Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Cardio-Renal Drug Products, HFD-110

Attention: Division Document Room

1451 Rockville Pike

Rockville, Maryland 20852-1420

NDA 21-437 Page 2

If you have any questions, please call:

Mr. Daryl Allis Regulatory Health Project Manager (301) 594-5309.

Sincerely,

(Securended electronic signature page)

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Natalia Morgenstern 12/17/01 04:31:13 PM



Food and Drug Administration Rockville MD 20857

APR 2 9 2002

Dear Dr.

Between March 20 and 26, 2002, Ms. Sharon Matson, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol of the investigational drug (eplerenone), performed for Searle/Pharmacia. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we find that, except for the inadequate identification of the person who recorded the source data, you were in basic compliance with pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Matson during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Antoine El-Hage, Ph.D.

Associate Director

Good Clinical Practice Branch I & II, HFD-46/47

Division of Scientific Investigations

Office of Medical Policy

Center for Drug Evaluation and Research

7520 Standish Place, Room 125

Rockville, MD 20855

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Headquarters (	Classification:
1)NAI	
	no response required
3)VAI- 1	response requested
4)OAI	
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failure to	adhere to protocol
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# Reviewer Note to Rev. Div. M.O.

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Inspection of this site revealed 16 subjects screened, 15 randomized, 5 dropped, and 10 completed. Overall, there was sufficient documentation at this site to assure that all audited subjects did exist, and were available for the duration of the study and that all enrolled subjects received the assigned study medication had clinical and laboratory parameters recorded, completed the study, and had their outcome captured as specified in the protocols and amendments. All subjects consented to the study.

Thus, all of the subjects at this site can be used for evaluation of Study Protocol # in support of NDA 21-437.

# DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297 Expiration Date: February 29, 2004.

# **USER FEE COVER SHEET**

# See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent-by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS	4. BLA SUBMISSION TRACKING NUMBER (ST	N) / NDA NUMBER
CD Coole II C	NDA 21-437	
G.D. Searle LLC		
4901 Searle Parkway		
Skokie, IL 60077	5. DOES THIS APPLICATION REQUIRE CLINIC	CAL DATA FOR APPROVAL?
	∑ YES □ NO	
	IF YOUR RESPONSE IS "NO" AND THIS IS I	OR A SUPPLEMENT, STOP HERE
·	AND SIGN THIS FORM.	
	IF RESPONSE IS "YES", CHECK THE APPRO	PRIATE RESPONSE BELOW:
	THE REQUIRED CLINICAL DATA ARE C	ONTAINED IN THE ADDI MATION
<b>{</b>		
	THE REQUIRED CLINICAL DATA ARE S	UBMITTED BY
2. TELEPHONE NUMBER (Include Area Code)	REFERENCE TO:	
( 847 ) 982-4751		
( 047 ) 302-4731	(APPLICATION NO. CONT	AINING THE DATA).
3. PRODUCT NAME	6. USER FEE I.D. NUMBER	
Eplerenone Tablets	4208	
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7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EX	CLUSIONS? IF SO, CHECK THE APPLICABLE EXC	LUSION.
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### DEPARTMENT OF HEALTH & HUMAN SERVICES



Public Health Service

Food and Drug Administration Rockville MD 20857

JUL 3 / 2002

### Dear Dr.

Between April 15 and 19, 2002, Ms. Traci Armand, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol of the investigational drug (eplerenone), performed for G. D. Searle. During our initial contact, we learned that all of the original study documents had been destroyed during a hailstorm that damaged the records beyond salvation. We understand that the records were stored at the and were, therefore, not under your direct control. However, we remind you that, as principal investigator, it is your responsibility to prepare and maintain study records. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to pertinent federal regulations governing your conduct of clinical investigations and the protection of human subjects. Because the original documents had been destroyed, the inspection was limited to photocopies of case report forms, laboratory reports, and electrocardiograms provided by the sponsor. We note that at the conclusion of the inspection, Ms. Armand presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

- 1. You did not prepare and maintain adequate and accurate case histories (21 CFR 312.62(b)).
  - a. There were no original source documents such as study worksheets and informed consent forms available.
  - b. No electrocardiograms were available for subject 55583.
- 2. You did not conduct the study in accordance with the approved protocol (21 CFR 312.60).
  - a. Subjects 55581, 55429, 55580, and 55583 were enrolled without using the revised, current inclusion and exclusion criteria.
  - b. Ten of 23 subjects participating in the study after the implementation of amendment #3 (sexual dysfunction questionnaire) did not have the form completed or documentation of the reason that the form was not completed.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Armand during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN: Field Classification: Refer to Center Headquarters Classification:1)NAI
Deficiencies noted:  X records availability (01)  X failure to adhere to protocol (05)  Deficiency codes: 1, 5
CC: HFA-224 HFD-110 Doc.Rm. NDA#21-437 HFD-110 Review Div.Dir. Throckmorton HFD-110 MO Marciniak HFD-110 PM Allis HFD-47 c/r/s/ GCP File #10624 HFD-47 Shibuya HFD-47 Storms HFR-SE-450 Debo HFR-SE-450 Wright HFR-SE-450 Armand r/d:(RS)(6/5/02) reviewed:AEH:(6/19/02) 6:\RS\NDA21-437/.
Reviewer Note to Rev. Div. M.O.  Upon scheduling this inspection, the field investigator learned that all of the original study documents had been destroyed because of a destructive hailstorm more than two years prior to the inspection. Apparently, the documents were water damaged and could not be preserved.  the study record custodian, decided to destroy the records. The field investigato inspected photocopied case report forms and laboratory and EKG data provided by the sponsor and found a few protocol violations. However, because none of the data from this site was verifiable, none of the data from Dr.  site should be considered in support of NDA 21-437.

I am concerned because Searle/Pharmacia did not report this data as unreliable. Dr.

hailstorm. We might consider contacting Searle to obtain a statement that the remainder of the

of the destruction of the records soon after the

Page 3 -

site did inform

data submitted in the application is verifiable.